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TRANSMITTAL FORM

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Application Number	09/660,568
Filing Date	September 11, 2000
First Named Inventor	David Ralph
Art Unit	1635
Examiner Name	Sean McGarry
Attorney Docket Number	UROC:014USD1

Total Number of Pages in This Submission

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
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- ☐ Reply to Missing Parts/ Incomplete Application
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- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☑ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☑ Other Enclosure(s) (please Identify below):
  Amended Appeal Brief
  Postcard

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Gina N. Shishima

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
David RALPH *et al.*

Serial No.: 09/660,568

Filed: September 11, 2000

For: DIAGNOSIS OF DISEASE STATE USING mRNA PROFILES IN PERIPHERAL LEUKOCYTES

Group Art Unit: 1635

Examiner: Sean McGarry

Atty. Dkt. No.: UROC:014USD1

AMENDED APPEAL BRIEF

I. REAL PARTY IN INTEREST 2
II. RELATED APPEALS AND INTERFERENCES 2
III. STATUS OF THE CLAIMS 2
IV. STATUS OF AMENDMENTS 2
V. SUMMARY OF CLAIMED SUBJECT MATTER 2
VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL 3
VII. ARGUMENT 3
A. Substantial Evidence Required to Uphold the Examiner's Position 3
B. Claims 9-10 and 64 Are Adequately Described 3
1. Claim 15 Is Separately Patentable 7
C. Claims 9-20 and 64 Are Enabled 7
1. Claim 15 Is Separately Patentable 9
D. Conclusion 9
VIII. CLAIMS APPENDIX 1 11
IX. EVIDENCE APPENDIX 2 14
X. RELATED APPEALS AND INTERFERENCES APPENDIX 3 15

PATENT

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AMENDED APPEAL BRIEF

MS Appeal Brief
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants hereby submit an Amended Appeal Brief in response to the Office Communication dated January 9, 2006, for which the one-month date for response is February 9, 2006.

This Amended Appeal Brief replaces the original Appeal Brief that was mailed to the Board of Patent Appeals and Interferences on December 23, 2004, in response to the Office Action dated March 24, 2004.

It is believed that no fees are due in connection with the filing of the Amended Appeal Brief; however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Commissioner is authorized to deduct said fees from Fulbright & Jaworski L.L.P. Account No.: 50-1212/UROC:014USD1.

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I. REAL PARTY IN INTEREST

The real party in interest is the assignee Urocor, Inc. in Oklahoma City, Oklahoma.

II. RELATED APPEALS AND INTERFERENCES

No related appeals or interferences are presently pending.

III. STATUS OF THE CLAIMS

Claims 1-73 were originally filed on September 11, 2000 in this case which is a divisional application of U.S. Patent Application serial number 09/046,894 filed on March 24, 1998. In a preliminary amendment filed concurrently with the divisional application, claims 1-7, 27-63 and 66-73 were canceled.

In response to a Restriction Requirement Dated February 13, 2003, claims 21-26 and 65 were withdrawn from examination.

Claims 9-26, 64 and 65 were pending in the final Office Action Dated March 24, 2004 ("Action"). Claims 21-26 and 65 were withdrawn from examination. Claims 9-20 and 64 were rejected. Thus, claims 9-20 and 64 are pending on appeal and are the subject of this appeal brief (Appendix A).

IV. STATUS OF AMENDMENTS

No amendments were filed subsequent to final rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The invention presently concerns a method of detecting a human disease state comprising the steps of a) detecting the quantity of a disease marker mRNA expressed in human peripheral blood, and b) comparing the quantity of said marker to the quantity expressed in

peripheral blood of a normal individual; wherein a difference in quantity of expression is indicative of a disease state. Specification at page 16, line 17 to page 17, line 13, and in originally filed claim 9.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1) Are claims 9-20 and 64 properly rejected as lacking an adequate written description under 35 U.S.C. § 112, first paragraph?

2) Are claims 9-20 and 64 properly rejected as lacking enablement under 35 U.S.C. § 112, first paragraph?

VII. ARGUMENT

A. Substantial Evidence Required to Uphold the Examiner's Position

As an initial matter, Appellants note that findings of fact and conclusions of law by the U.S. Patent and Trademark Office must be made in accordance with the Administrative Procedure Act, 5 U.S.C. § 706(A), (E), 1994. *Dickinson v. Zurko*, 527 U.S. 150, 158 (1999). Moreover, the Federal Circuit has held that findings of fact by the Board of Patent Appeals and Interferences must be supported by "substantial evidence" within the record. *In re Gartside*, 203 F.3d 1305, 1315 (Fed. Cir. 2000). In *Gartside*, the Federal Circuit stated that "the 'substantial evidence' standard asks whether a reasonable fact finder could have arrived at the agency's decision." *Id.* at 1312.

Accordingly, it necessarily follows that an Examiner's position on Appeal must be supported by "substantial evidence" within the record in order to be upheld by the Board of Patent Appeals and Interferences.

B. Claims 9-10 and 64 Are Adequately Described

Claims 9-20 and 64 are rejected under the first paragraph of §112 as lacking an adequate written description. The Action contends that the claims contain subject matter that was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time of the application was filed, had possession of the claimed invention. In particular, the Action argues that the specification does not identify a representative number of disease markers to show possession of the claimed invention. Action at pages 2-3 and page 5.

The Federal Circuit has stated that the test for the written description requirement is "whether the application relied upon 'reasonably conveys to the artisan that the inventor had possession at the time of the later claimed subject matter.'" *In re Daniels*, 144 F.3d 1452, 1456, 46 USPQ2d 1788, 1790 (Fed. Cir. 1998). *See also Markman v. Westview Instruments, Inc.* 52 F.3d 967, 34 USPQ 2d 1321 (Fed. Cir. 1995) (en banc) ("Claims must be read in view of the specification, of which they are a part."). In rejecting a claim under the written description requirement of 35 U.S.C. §112, first paragraph, the Examiner has the initial burden of presenting evidence or reasons why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined in the claims. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). Accordingly, the Examiner is required: (1) to set forth the claim limitation not described; and (2) to provide reasons why a person skilled in the art would not have recognized the description of the limitation in view of the disclosure of the application as filed. *Interim Guidelines for the Examination of Patent Applications Under 35 USC 112, Paragraph 1*, Chisum on Patents, vol. 3, §7.04[1][c].

The written description requirement has been extensively addressed by the Federal Circuit. In particular, the Federal Circuit has stated that "[t]he written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she]

invented what is claimed.'" *Union Oil Co. of California v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 USPQ 2d 1227, 1232 (Fed. Cir. 2000).

Appellants point out that claims 9-20 and 64 are directed to a ***method of detecting*** the quantity of a disease marker mRNA in the peripheral blood and comparing the quantity of the disease marker in a sample with the quantity of the disease marker in normal individuals' blood. The amended claims do not claim a disease marker, but claim a method of detecting disease states by analysis of peripheral blood. The Action admits that Appellants have provided methods of identifying disease markers. Action at page 5 and page 6. The Action states that the various disease markers disclosed in the application are insufficient, but fails to provide adequate reasoning or support as to why this is so.

The specification provides sufficient description of the method to convey to one of skill in the art that the inventors had possession of the claimed method for detecting a human disease state. For example, claim 9 calls for detecting the quantity of a disease marker mRNA expressed in human peripheral blood, and comparing the quantity of said marker to the quantity expressed in peripheral blood of a normal individual, where the difference in quantity of expression is indicative of a disease state. In addition to the description provided by the originally filed claims, the specification provides a more than sufficient written description of the claimed method (specification at least at page 8, lines 10-27; pages 85-92; and in the examples on pages 100-161). The specification states:

> "The instant invention addresses the problem of diagnosing human disease states by detecting a secondary response to a given disease state that may be measured in peripheral blood samples. A preferred embodiment involves monitoring gene expression in peripheral leukocytes of the immune system. A number of disease states are capable of producing an immune system response, such as asthma, lupus erythromatosis, rheumatoid arthritis, multiple sclerosis , myasthemia gravis, autoimmune thyroiditis, ALS (Lou Gehrig's disease), interstitial cystitis and

> prostatitis. The methods disclosed herein may be suitable for detection of these diseases, as well as cancers from a variety of tissue sources." Page 8, lines 20-27.

The Action's arguments based on description of cDNA structure are irrelevant. Furthermore, the specification provides exemplary methods for detection and quantification of RNA (pages 85 to 100). The specification also provides specific examples that describe the use of the claimed method for the detection of disease markers for a metastatic cancer, *i.e.*, metastatic breast or prostate cancer (pages 100-161).

The unrebutted presumption is that one of skill in the art would have understood that the inventors were in possession of the claimed method of detecting a human disease state(s) as originally claimed. The steps of the ***diagnostic method*** are clear. While the claims may encompass the use of compositions not specifically exemplified or identified, the claims do require that there is a difference in the expression of the disease marker mRNA relative to diseased and normal peripheral blood. The claims encompass a method of diagnosis and not a disease marker composition or a method of identifying a disease marker. Appellants emphasize that the present claims are method of detection claims, and thus, as evinced by the foregoing, one of skill in the art would reasonably conclude that the inventor had possession of a method of detecting a human disease state. The method comprising detecting the quantity of a disease marker mRNA expressed in human peripheral blood, and comparing the quantity of said marker to the quantity expressed in peripheral blood of a normal individual, where a difference in quantity of expression is indicative of a disease state.

The Federal Circuit in *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991), cited a Supreme Court opinion that the second requirement of paragraph 112 was:

> "to put the public in possession of what the part claims as his own invention, so as to ascertain if he claims anything that is in common use, or is already known, and to guard against prejudice or injury from the use of an invention which the party

> may otherwise innocently suppose not to be patented. It is, therefore, for the purpose of warning an innocent purchaser, or other person using . . . [the invention], of his infringement of the patent; and at the same time, of taking from the inventor the means of practicing upon the credulity or the fears of other persons, by pretending that his invention is more than what it really is, or different from its ostensible objects, that the patentee is required to distinguish his invention in his specification."

Evans v. Eaton, 20 U.S. (7 Wheat.) 356 (1822). Appellants' specification makes clear what the invention is so as to put the public on notice. There can be no dispute that they have described what they now claim. The originally filed claims provide literal support for the presently rejected claims and, as discussed above, Appellants set forth sufficient details of the method claimed.

In view of the arguments presented above, Appellants respectfully request this rejection be withdrawn.

1. Claim 15 Is Separately Patentable

Claim 15 recites a method of detecting a human disease state where the disease state is prostate cancer.

Because this amendment provides an additional limitation that addresses the Action's concern relating to identifying markers for disease states, this claim is separately patentable. The Action admits that the specification provides adequate written description for prostate cancer. Action at pages 5-6. Accordingly, Appellants respectfully request that this rejection be withdrawn.

C. Claims 9-20 and 64 Are Enabled

Claims 9-20 and 64 are rejected under the first paragraph of §112 as lacking an enabling disclosure. The examiner contends it would require undue experimentation to practice the full scope of the claimed invention.

To satisfy the enablement requirement of 35 U.S.C. 112, first paragraph, the claimed invention must be described in such a way as to contain sufficient information regarding the claimed invention as to enable one skilled in the art to make and use the claimed invention without undue experimentation. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is satisfied. Applicants note, in regard to basing an enablement rejection on a reference to a written description rejection, that the enablement and written description requirements are distinct (*Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1114 (Fed. Cir. 1991)).

In order for the Action to put forth an enablement rejection, a reasonable basis to question the enablement must be provided. (*In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1509, 1513 (Fed. Cir. 1993)). The Action fails to set forth a sufficient reason why one of skill in the art would not be able to detect a human disease state by a) detecting the quantity of a disease marker mRNA expressed in human peripheral blood; and b) comparing the quantity of said marker to the quantity expressed in peripheral blood of a normal individual; wherein a difference in quantity of expression is indicative of a disease state, as described in the present claims and specification. Applicants note again, that claims are directed to a method of detection not a disease marker mRNA.

Applicants provide several working examples of the claimed methods. For example, the specification describes exemplary methods that detect human metastatic breast and metastatic prostate cancer by detecting the quantity of a IL-8 mRNA expressed in human peripheral blood from either metastatic breast cancer or metastatic prostate cancer patients; and comparing the quantity of the IL-8 marker to the quantity of IL-8 expressed in peripheral blood of normal

individuals; wherein a difference in quantity of expression is indicative of a disease state (pages 108-112 and 136-146). The Action provides no reason why IL-8 or other disease markers would not be a viable marker for other cancers or other disease states. Particularly, since IL-8, for example, is expressed in peripheral blood cells in response to the disease condition and is not itself specific for a diseased cell. One of skill in the art would readily be able to extend, without undue experimentation, the claimed methods to other disease markers that are indicative of a disease state when there is a difference in the quantity of disease marker mRNA expressed in the peripheral blood.

In view of the arguments presented above, Appellants respectfully request this rejection be withdrawn.

1. Claim 15 Is Separately Patentable

Claim 15 recites a method of detecting a human disease state where the disease state is prostate cancer.

Because this amendment provides an additional limitation that addresses the Action's concern relating to identifying markers for disease states, this claim is separately patentable. The Action admits that the specification provides adequate written description for prostate cancer. Action at pages 5-6. Further, the Examples in the specification show in detail how to use prostate cancer markers to carry out the method of claim 15 (pages 114-137). Accordingly, Appellants respectfully request that this rejection be withdrawn.

D. CONCLUSION

For the above-argued reasons, Appellants respectfully request that the rejection of the claims be withdrawn. Appellants have provided arguments that overcome the pending rejections. Appellants respectfully submit that the Office Action's conclusion that the claims

should be rejected is unwarranted. It is therefore again requested that the Board overturn the Action's rejections.

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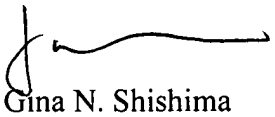
Respectfully submitted,



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Date: February 7, 2006

VIII. CLAIMS APPENDIX 1

1-8. (canceled)

9. (previously presented) A method of detecting a human disease state, comprising the steps of::

a) detecting the quantity of a disease marker mRNA expressed in human peripheral blood; and

b) comparing the quantity of said marker to the quantity expressed in peripheral blood of a normal individual;

wherein a difference in quantity of expression is indicative of a disease state.

10. (original) The method of claim 9, wherein said mRNA is amplified by an RNA polymerase reaction.

11. (original) The method of claim 9, wherein said mRNA is amplified by reverse transcriptase polymerase chain reaction or the ligase chain reaction.

12. (previously presented) The method of claim 9, wherein said detecting is by RNA fingerprinting, branched DNA or a nuclease protection assay.

13. (previously presented) The method of claim 9, wherein the disease state is metastatic cancer, asthma, lupus erythromatosis, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, autoimmune thyroiditis, ALS (Lou Gehrig's disease), interstitial cystitis or prostatitis.

14. (previously presented) The method of claim 9, wherein the disease state is metastatic cancer.

15. (original) The method of claim 14, wherein the metastatic cancer is metastatic prostate cancer.

16. (original) The method of claim 14, wherein the metastatic cancer is metastatic breast cancer.

17. (original) The method of claim 9, in which said mRNA comprises one or more of the sequences or the complements of the sequences disclosed herein as SEQ ID NO: 1, SEQ ID N0:2, SEQ ID N0:3, SEQ ID NO:29, SEQ ID N0:34, SEQ ID NO:48 or SEQ ID NO:49.

18. (previously presented) The method of claim 9 in which said marker is a product of an interleukin 8 (IL-8) or interleukin 10 (IL- 10) gene.

19. (original) The method of claim 9, further comprising the steps of

a) providing primers that selectively amplify said disease state marker;

b) amplifying said nucleic acid with said primers to form nucleic acid amplification products;

c) detecting said nucleic acid amplification products; and

d) measuring the amount of said nucleic acid amplification products formed.

20. (original) The method of claim 19 in which said primers are selected to specifically amplify a nucleic acid having a sequence comprising SEQ ID NO:1, SEQ ID N0:2, SEQ ID NO:3, SEQ ID N0:29, SEQ ID NO:34, SEQ ID N0:48 or SEQ ID NO:49.

21. (withdrawn) The method of claim 8, wherein said marker is a polypeptide.

22. (withdrawn) The method of claim 21, wherein said polypeptide is encoded by a nucleic acid sequence comprising the sequence disclosed herein SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO: ID NO:3, SEQ ID N0:29, SEQ ID NO:34, SEQ ID NO:48 or SEQ ID N0:49.

23. (withdrawn) The method of claim 21, wherein said detection is by an antibody immunoreactive with said marker.

24. (withdrawn) The method of claim 21, wherein said polypeptide is encoded by an IL-8 or IL-I0 gene.

25. (withdrawn) The method of claim 8, wherein said marker is a product of the IL-8 gene and wherein said comparison is between two alternatively spliced forms of an IL-8 gene product.

26. (withdrawn) The method of claim 24, wherein the quantity of IL-8 polypeptide in peripheral blood is measured using an in vitro bioassay that detects an IL-8 mediated biological process.

27.- 63. (cancelled)

64. (original) The method of claim 19, in which said primers are selected to specifically amplify a nucleic acid product of the IL- 10 gene.

65. (withdrawn) The method of claim 24, wherein the quantity of IL-10 polypeptide in peripheral blood is measured using an in vitro bioassay that detects at least one IL-10 mediated biological process.

Claims 66-73 (cancelled)

IX. EVIDENCE APPENDIX 2

None.

X. RELATED APPEALS AND INTERFERENCES APPENDIX 3

None.